and encoding at least one part of at least one of a penton or hexon protein, said penton or hexon protein having lower antigenicity relative to penton or hexon proteins of the first adenovirus serotype and resulting in a viral particle having lower antigenicity;

inserting into said recombinant vector at least one second nucleic acid from said nucleic acid library, said at least one second nucleic acid obtained from the first adenovirus serotype and encoding at least one functional part of a fiber protein having the desired host range;

inserting said gene of interest into said recombinant vector;

providing at least one packaging cell;

transfecting said recombinant vector into said at least one packaging cell; and

producing chimeric viral particles.

Remarks

The Office Action mailed 24 October 2000 has been received and reviewed. Claims 1, 2 and 9-11 are pending in the application. All stand rejected. The application is to be amended as previously set forth, to include the addition of new claims 13-32. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. Examiner Interview:

Applicants would first like to thank Examiner Lee and her Supervisory Primary Examiner Clark for the courtesy extended during the interview of 17 November 2000. Applicants considered the interview helpful in clarifying the issues and understanding the rejections, as evidenced by the summary of the interview, *i.e.*,

> Examiner and Applicant discussed the breadth of the claims corresponding to Crystal et al. U.S. Patent #6,127,525 and specifically claims to the methodology of the application. Discussed ways to distinguish the claimed invention such as the library.

2. Information Disclosure Statement

The Examiner placed in the file, but did not consider, the Supplemental Information

Disclosure Statement filed by applicants on 1 August 2000. The Examiner stated that applicants need to provide a list of the cited references referenced on a Form PTO-1449 in order to comply with the provisions of 37 CFR 1.98(a)(1). As discussed at the interview, however, the particular "references" are in fact co-pending application naming a common inventor. The applications and their claims are (or were) pending in the Office. The applications are identified so that the Office can ensure that the various applications do not claim the same subject matter (*e.g.*, to prevent double patenting or obviousness-type double patenting). *See*, M.P.E.P. §§ 804 & 2001.06(b). Under such circumstances, a Form PTO-1449 would not seem needed. However, if the Examiner insists, applicants will provide the Form PTO-1449.

As was also discussed at the Interview of 17 November 2000, applicants additionally submit via Form PTO-1449 a list of prior art cited by the new primary reference U.S. Patent 6,127,525 to Crystal et al. ("Crystal").

Applicants note, however, that three of the references cited by Crystal have not been included in the Form PTO-1449. The references not listed on the Form PTO-1449 are: Michael et al., presented at Adenovirus Workshop: St. Andrews University, p. 52 (Jul. 13-15, 1995); Abstract of Grant Application No. 1 P01 HL51746-01UB: 0004, "Gene Therapy For Cystic Fibrosis", Falck-Pedersen, submitted to the National Institutes of Health, (1994); and Watkins et al., presented at Keystone Symposium on Molecular and Cellular Biology, Abst. No. 336 (Taos: NM, Feb. 22-28, 1996). Despite Applicants' extensive efforts, these references could not be located.

3. 35 U.S.C. § 102(e) Rejection of Claims 1, 2 and 9-11 over U.S. Patent 6,127,525 to Crystal et al.

Claims 1, 2 and 9-11 stand rejected under 35 U.S.C. § 102(e) as anticipated by Crystal. Applicants have amended independent claims 1, 2 and 9, and respectfully traverse the rejection as hereinafter set forth.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown

in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Crystal describes a chimeric adenoviral coat protein having a decreased ability or inability to be recognized by a neutralizing antibody directed against the corresponding wild-type adenovirus coat protein. Applicants respectfully submit, however, that claims 1, 2 and 9-11 should be allowed over the 35 U.S.C. § 102(e) anticipation rejection because Crystal fails to expressly or inherently describe a chimeric adenoviral vector and methods of producing a chimeric adenoviral vector as presently claimed by applicants.

Crystal is drawn to the production of chimeric adenovirus that exhibits a decreased ability or inability to be recognized by a neutralizing antibody. (Crystal, col. 4, lines 23-30). To accomplish the aims of the invention, Crystal discloses that a region of an adenoviral coat protein is rendered less immunogenic by deletions, insertions, and/or substitutions in various coat protein regions. In particular, Crystal discloses various deletions, substitutions, and insertions in adenoviral hexon and fiber proteins which are designed to decrease immunogenicity. (Crystal, col. 6, line 21 to col. 11, line 62). Adenoviral vectors comprising a chimeric coat protein are disclosed, for example, in Crystal, col. 14, line 58 to col. 18, line 47. Crystal further discloses methods of making chimeric adenoviral vectors in Examples 2, 4 and 5 of the Crystal specification.

In regard to independent claim 1 and claim 11 which depends therefrom, applicants respectfully submit Crystal does not describe the individual claim elements or element combination reciting:

> at least a part of a fiber protein of a first adenovirus serotype, said at least a part of a fiber protein adapted to provide the chimeric adenovirus with a desired tropism to a plurality of target cells in a host; and
>
> at least a part of a penton or hexon protein from a second adenovirus serotype, the second adenovirus serotype having a lower relative tropism to the plurality of target cells than that of the chimeric virus, the second adenovirus serotype having less antigenicity in a human than the first adenovirus serotype resulting in a chimeric adenovirus that is less antigenic in a human than the first adenovirus serotype.

More specifically, applicants respectfully submit that Crystal does not describe "at least a

part of a fiber protein adapted to provide the chimeric adenovirus with a desired tropism to a plurality of target cells in a host". Rather, applicants submit that Crystal is narrowly drawn to chimeric adenovirus coat proteins configured for reduced antigenicity. In this regard, the "Summary of the Invention" offered by Crystal is instructive:

> The present invention provides a chimeric adenovirus coat protein (particularly a chimeric adenovirus hexon protein) comprising a nonnative amino acid sequence. The chimeric adenovirus coat protein is not recognized by, or has a decreased ability to be recognized by, a neutralizing antibody directed against the corresponding wild-type (i.e., native) coat protein. The chimeric adenovirus coat protein enables a vector (such as an adenovirus) comprising the corresponding protein to be administered repetitively, or to be administered following administration of an adenovirus vector comprising the corresponding wild-type coat protein. It also enables a vector (such as an adenovirus) comprising the chimeric protein to be administered and effect gene expression in the case where there are preexisting neutralizing antibodies directed against the wild-type adenovirus coat protein. . . . .

(Crystal, col. 3. line 57 to col. 4 line 7).

Thus, while Crystal teaches to make a fiber protein less immunogenic by, for example, removing one or more epitopes on the fiber protein (e.g., col. 4, lines 57-65), applicants could find no mention in Crystal of a chimeric adenovirus comprising a fiber protein adapted to provide the chimeric adenovirus with a desired tropism. Applicants further submit that Crystal teaches away from the subject limitation in that Crystal narrowly focuses on immunogenicity to the exclusion of a desired tissue tropism.

Applicants secondly submit that Crystal does not teach the claim 1 combination of elements drawn to: (1) a fiber protein of adapted to provide the chimeric adenovirus with a desired tropism to a plurality of target cells in a host, and (2) a penton or hexon protein from an adenovirus serotype differing from the serotype of the fiber protein, wherein the second adenovirus serotype has a lower relative tropism to the plurality of target cells than that of the chimeric virus. In this regard, applicants could find no discussion or recognition in Crystal of a chimeric adenovirus which combines the desired host range properties of a fiber protein of a first adenoviral serotype with the desired immunogenic properties of a hexon or penton protein of a second adenoviral serotype. Applicants further submit that Crystal does not contemplate the recited relationship between the

relative tropisms of the produced chimeric adenovirus and the second adenovirus serotype of the selected penton or hexon protein.

With regard to presently amended claim 2, applicants submit that Crystal does not expressly or inherently describe a recombinant vector with an inserted gene sequence which encodes at least a functional part of a fiber protein of an adenovirus serotype different from the serotype of an inserted gene sequence encoding a hexon or penton protein, wherein the gene sequence encoding the fiber protein is adapted to exhibit a desired tropism to a plurality of target cells in a host. As previously discussed, Crystal teaches selecting a fiber protein for its immunogenic properties in a vector, and does not discuss adapting a fiber protein to exhibit a desired tropism to targeted cells.

With regard to presently amended claim 9, and claim 10 that depends therefrom, applicants respectfully submit that Crystal does not describe the method step reciting: "selecting a fiber protein for a desired tropism to targeted tissue of a host, said fiber protein derived from the second adenovirus serotype". (Emphasis added). Applicants submit that while Crystal teaches selecting a fiber protein for immunogenicity, Crystal does not expressly or inherently describe selecting a fiber protein for inclusion in a chimeric adenovirus on the basis of its tropism to targeted host tissue.

In view of the amendments to independent claims 1, 2 and 9, applicants respectfully submit that Crystal does not describe each and every element of claims 1, 2 and 9-11. Applicants accordingly respectfully request that the anticipation rejections be withdrawn, and claims 1, 2 and 9-11 allowed.

4. Sequence Listing

The Examiner stated that the sequence listing of the present application fails to comply with the nucleotide and/or amino acid sequence listing requirements of 37 CFR 1.821-1.825.

Applicants have enclosed a corrected Sequence Listing in paper and electronic copy in compliance with the requirements of 37 C.F.R. §§ 1.821-1.825.

5. New Claims

As was discussed in the Examiner Interview of 17 November 2000, applicants submit that

the subject matter of new claims 13-32 is supported by the as-filed specification and drawings, and does not add any new matter to the application. For example, the claim limitations drawn to a nucleic acid library, as presently recited in newly added independent claims 13, 28 and 32, are supported by pages 8-11 of the application specification.

Conclusion

In view of the Examiner Interview, amendments, and remarks presented herein, applicants respectfully submit that the amended and newly added claims define patentable subject matter. Allowance of all of the pending claims is therefore respectfully requested. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Date: January 24, 2001

Enclosures: Corrected Sequence Listing (paper and electronic copy)
Statement Under 37 C.F.R. §§ 1.821 (f)&(g)
Second Supplemental Information Disclosure Statement
Form PTO-1449 with copies of cited documents